

## Salutary lessons from the Collaborative Eclampsia Trial

Magnesium sulphate now can be confidently recommended as the anticonvulsant of choice for eclampsia. The results of the Collaborative Eclampsia Trial (1) have shown that although its mode of action is not understood, magnesium sulfate has clear advantages when compared with both diazepam and phenytoin. Recurrent seizures were 2 to 3 times less frequent, and other serious outcomes were also substantially reduced in comparison with phenytoin. These findings have clear implications for clinical practice, but other salutary lessons can be learned from the planning and execution of this study.

First, the trial emphasises the need for evidence about the effects of health care. When the original report of the trial was published, the editor observed, "Today's report is a triumph for the trialists; but what a scandal that we had to wait 70 years for the answer." Since 1925, when an American obstetrician reported about an uncontrolled case series of 20 women with eclampsia who were treated with magnesium sulphate, arguments have raged about how to care for women with eclamptic seizures. For 70 years, the proponents of various drugs and drug cocktails have hurled disdainful abuse at each other from separate mountain tops, secure in the knowledge that no strong evidence existed that could undermine any one of their multitude of conflicting opinions (2). Perhaps the greatest opprobrium should be reserved for the journals and investigators who, since 1987, have reported small, poorly controlled studies encouraging the notion that phenytoin should be used not only for the treatment of eclamptic fits but also for prophylaxis (3-6).

During a total period of just over 5 years, far more has been achieved through the collective efforts of 27 centres in 9 developing countries (some that had little or no

previous research experience) than has been accomplished during more than half a century of small-scale, poorly controlled, individualistically driven investigative tinkering by others, including many people in the developed world who believe they deserve to be regarded as serious investigators. This lack of scientific and professional self-discipline in the developed world, particularly the unwillingness to collaborate in studies of sufficient size, has had substantial human costs. As noted in the report of the trial, "From magnesium sulphate first being suggested for women with eclampsia (in 1906) to the introduction of diazepam (in 1968), a possible 33 million women would have had an eclamptic convulsion and 3 million of them may have died. Up to 1987, when phenytoin was introduced, a further 9 million women possibly had an eclamptic convulsion and one million died" (1).

How did this landmark trial ever take place? The plan emerged during discussions between a visiting research fellow from a developing country and staff at a health services research unit in a developed country. Best estimates suggested that the case fatality rate of eclampsia was high everywhere; that, worldwide, as many as 50 000 maternal deaths associated with eclampsia might occur each year; that 99% of these deaths involve women in developing countries (7); and that routine antenatal care could not guarantee prevention (8). These considerations argued strongly for a trial to address the therapeutic uncertainties surrounding a condition that poses a serious threat to maternal survival in the developing world, and that the study should therefore be organised in developing countries. Accordingly, a protocol was developed for a collaborative trial—to be run (initially) in Spanish, and to involve a network of hospitals in Latin America that were identified and supported by centres

that were receiving long-term institutional support from the World Health Organisation (WHO) (9).

A second salutary lesson from the trial is that the challenges facing those wishing to generate reliable evidence about health care are not necessarily just scientific. Recruitment to the trial started after permission was granted by the research ethics committees answerable to the populations in which the study was to be run. Consent was sought from relatives when possible or from the women themselves when they had regained full consciousness. Despite this, the WHO Committee on Research Involving Human Subjects blocked an award of funds for the trial for 6 months, insisting that "informed consent" must be obtained *before trial entry* from the unconscious and semiconscious participants in a study that was comparing three anticonvulsant drugs that were already in widespread use! As is too often the case with research ethics committees, the WHO Committee's lines of accountability for this impractical and, frankly, dangerous advice were unclear. Initial funding was eventually forthcoming from WHO, however, and subsequent support from the UK Overseas Development Administration meant that it was possible to extend the trial to centres in Africa and India. An eventual total of 1687 women participated in the trial—97% of the eligible women admitted to the participating centres—and data were available for 99.6% of these.

A further salutary lesson, and a matter for particular satisfaction, is that a trial designed to address important practical problems in the developing world has not only challenged assumptions (10) about the pathophysiology of eclamptic convulsions (11) but has also been deemed by first-world investigators to be "the most important obstetric trial of the 20th century" (12), "a landmark in the development of rationale therapies for eclampsia" (13), and

that it has set "new standards for vision and ambition in clinical trials in perinatal medicine" (12). In addition to clarifying which anticonvulsant should be adopted as standard, for example, the trials use of "shoe-box" eclampsia packs (which contain everything required to start emergency treatment of eclampsia) seems likely to be widely emulated in routine practice.

Important future challenges remain, however. Within the developed world, the most important of these seems likely to be the prevention of unwarranted extrapolation of the results of the trial to prophylactic use of magnesium sulphate in pre-eclampsia. Good evidence now exists that phenytoin should not be used prophylactically in severe pre-eclampsia (also reported in this issue [14]), but no evidence exists that the potential benefits of prescribing magnesium sulphate prophylactically in these circumstances outweigh the potential risks of this policy. Research is now required to address this question.

The most important and pressing challenge, however, is to ensure that the evidence generated by the trial has an effect on the care of the women in the developing world who have most to benefit from the knowledge that magnesium sulphate is the anticonvulsant of choice. Just before the report of the trial was published,

WHO disseminated the following advice: "Anticonvulsants and sedatives are effective in the management of eclampsia *and pre-eclampsia* [italics ours]. To prevent the occurrence of eclamptic seizures, three drugs are proposed: magnesium sulphate, diazepam and the 'lytic cocktail' consisting of promethazine, chlorpromazine, and pethidine" (15). Not only did this advice (which has subsequently been altered) ignore the basis for doing the Collaborative Eclampsia Trial (uncertainty about how best to treat the condition), it also contradicted statements made in WHO's own progress report of relevant research (16) and ignored evidence suggesting that "the lytic cocktail" is harmful (17)!

Clearly, then, there are wide-ranging implications of the Collaborative Eclampsia Trial, not only for the clinical care of pregnant women, but also for those doing, overseeing, funding, and publishing research, and for those with responsibilities for promulgating safe and effective health policies. Let us hope that the lessons will be learned before too many more women die unnecessarily.

*Iain Chalmers*  
UK Cochrane Centre  
Oxford, UK

*Adrian Grant*  
Health Services Research Unit  
Aberdeen, UK

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